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Large amplitude motion affects cleavage reaction barrier in HIV protease

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The role of protein flexibility on catalytic activity is a controversial subject. To shed light into this topic we propose the use of configurations generated using normal mode analysis (NMA) and low temperature dynamics [1] of substrate bound HIV protease (HIP-PR) to investigate the cleavage reaction using QM/MM (QM/Molecular Mechanics) methods. HIV-PR is a major drug target used in highly active anti-retroviral therapy (HAART), where protease inhibitors are commonly used. Our aim is to understand how large-scale protein motion can affect HIV-PR catalytic activity, and thus protein function.

Starting from a substrate bound crystal structure of HIV-PR (PDB assertion code 1KJF) we generate a large ensemble of structures using NMA (250 configurations) employing a recently proposed protocol [2]. Emphasis is placed on 20 states with largest displacements. Selected relevant structures were used to investigate the barrier for the substrate cleavage reaction using PM6 (a semi-empirical method). We used for the QM calculations an active site made of 18 amino acids in addition to 5 water molecules.

Our result suggests a strong dependency between the initial configuration selected and the resulting amino acid cleavage barrier. Particularly interesting was the fact that the barrier for a subset of 32 structures was up to 10kcal.mol^{-1} lower than the one obtained from the crystal structure configuration, producing results much closer to experiments.

Key-words: QM/MM, NMA, HIV-PR, Large amplitude motion, enzymatic reactions.
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References:

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